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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,182	03/23/2001	Darwin J. Prockop	53844-5019	5852

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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 05/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/816,182	PROCKOP ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *4-8 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed February 14, 2005 (hereinafter referred to as "the response") has been entered. Claims 1 and 9 have been amended.

Claims 1-10 remain pending in the instant application.

Claims 4-8 and 10 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Election was made **without** traverse in the response filed October 23, 2003. The elected invention is drawn to a population of small and rapidly self-renewing stem (RS) cells.

Accordingly, Claims 1-3 and 9 are examined herein.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 14, 2005 has been entered.

The rejection of Claim 9 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendment of the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1-3 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants are reminded that the written description requirement is severable from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), *cert.* denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991). The Federal Circuit, while acknowledging that some of its cases concerning the written description requirement and the enablement requirement are confusing, reaffirmed that under 35 U.S.C. 112, first paragraph, the written description requirement is separate and distinct from the enablement requirement and gave an example thereof. An invention may be described without the disclosure being enabling (e.g., a chemical compound for which there is no disclosed or apparent method of making), and a disclosure could be enabling without describing the invention (e.g., a specification describing a method of making and using a paint composition made of functionally defined ingredients within broad ranges would be enabling for formulations falling within the description but would not describe any specific formulation). See *In re Armbruster*, 512 F.2d 676, 677, 185 USPQ 152, 153 (CCPA 1975).

As amended, Claim 1 is directed to a population of cells enriched for human small and rapidly self-renewing stem cells (RS), wherein about 95% of the cells in said population are RS cells, further wherein the cells within said population express one or more polypeptides selected from the group

consisting of VEGF receptor-2 (FLK-1), TRK (an NGF receptor), transferrin receptor, and annexin II (lipocortin 2).

The claims cover a wide variety of cell compositions, having widely variant phenotypes.

The term "RS cell" is not defined in the specification. Therefore, in interpreting the present claims, the term "RS cell" is construed to impart no particular physical structure upon the claimed composition. Although the specification discloses that a population of cells comprising 95% "RS cells" (page 2, lines 16-18) was obtained by filtering day 14 cultures[1] of MSCs through a 10 micron filter and further that the RS cells obtained by this filtering method are about 7 microns in diameter (page 5, line 13), the **claimed** cell population is not limited to cells that are 7 microns in diameter and thus covers RS cells of any size. Likewise, although the specification discloses that RS cells express FLK-1, TRK, transferrin receptor (CD71), **and** annexin II (lipocortin 2), the **claimed** cell population is not limited to RS cells that express **all 4** of these proteins. As claimed, the RS cells need not express **any** of these four proteins.

The claims are constructed in such a way that the RS cells referred to within the claim need not express **any** of the 4 polypeptides mentioned in Claim 1. For example, the remaining 5% of the claimed cell population may include endothelial cells that express FLK-1, which would be sufficient to satisfy the claim limitation requiring that "cells within said population express ... FLK-1." As long as there are a few cells within the population that express one of the recited polypeptides, the RS cells need not express any of the 4 polypeptides mentioned. Thus, the claims cover cell compositions comprising RS cells that do not express any of the 4 polypeptides mentioned, but the specification does not describe RS cells that do not express the 4 polypeptides. On the contrary, the specification **only** discloses RS cells that express **all 4** of the polypeptides recited in Claim 1. The RS cells described in the instant specification are of the type FLK-1$^+$, TRK$^+$, transferrin receptor$^+$, annexin II$^+$.

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[1] It is further noted that day 14 cultures contain very few RS cells (see Figure 3).

The claims also cover cell compositions that include RS cells expressing a wide variety of different combinations of the polypeptides recited in the claims, and thus covers cells having widely variant phenotypes. For example, the claims cover cell compositions that include RS cells that are of the type FLK-1$^-$, TRK$^-$, transferrin receptor$^+$, annexin II$^+$, but the specification does not describe RS cells that do not express FLK-1 and TRK. On the contrary, the specification only describes RS cells that express all four proteins.

Likewise, the claims cover cell compositions that include cells expressing a wide variety of different combinations of the polypeptides recited in Claim 2, thus covering cells having widely variant phenotypes, most of which are not described in the specification.

With regard to Claim 3, the claim covers cell compositions that include cells that express any 29 polypeptides not expressed in mMSC, but the specification only describes a single cell type that expresses one specific array of 29 polypeptides not expressed in mMSC.

Likewise, with regard to Claim 9, the claim covers a wide variety of cell compositions, with widely variant phenotypes not described in the specification.

Claims 3 and 9 further recite the term "large, more mature marrow stromal cells (mMSC)" which is also not defined in the specification and therefore is not construed to refer to a specific cell type having any particular structural or functional properties. Although the specification provides some characterization of cells referred to as mMSC, the term "mMSC" is not **defined** as referring to cells having the particular protein expression profile discussed in the specification and it is improper to import characteristics presented in the specification into the claims.

Thus, the claims are directed to a great variety of cell compositions that are not described in the instant specification.

The limited information provided in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the wide variety of cell

compositions encompassed by the claims and therefore the written description requirement is not satisfied for the claimed invention.

At page 8, paragraph 1 of the response, Applicants assert that the amendment deleting the term "homogenous" and adding the limitation "wherein about 95% of the cells in said population are RS cells" obviates the rejection. However, for the reasons discussed above, the claims as amended do not satisfy the written description requirement, since the claims are directed to a very large genus of cell compositions, while only a single species within the claimed compositions is described in the specification. Further, since the term "RS cell" is not defined in the specification, the newly added limitation "wherein about 95% of the cells in said population are RS cells" does not impart any particular structure to the cells that make up the composition. Moreover, since the specification uses the term "RS cells" to refer to a heterogenous population of cells, much as the term "blood cells" refers to multiple cell types, as discussed in the prior Office Action of 8/11/04 (at page 5), the newly added limitation does not limit the claimed composition to one that is composed of primarily a single cell type.

At page 8, paragraph 2 of the response, Applicants assert that there is ample written description in the specification for claims to a population of RS cells, wherein about 95% of the cells in the population are RS cells. However, given that the term "RS cell" is not defined in the specification, using the term in the claims does not impart any particular structural or functional properties to the cells that make up the composition. As discussed in detail above, given the present claim language, the RS cells recited in the claim need not express any of the polypeptides recited in the claims. Furthermore, the term "RS cell" does not refer to a single cell type.

Enablement

Claims 1-3 and 9 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a population of cells enriched for human small and rapidly self-renewing stem

cells (RS), wherein about 95% of the cells in said population are RS cells, and further wherein said RS cells express VEGF receptor-2 (FLK-1), TRK, transferrin receptor, **and** annexin II, does not reasonably provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As discussed above, the claims cover a great variety of cell compositions having widely variant phenotypes, but the specification only describes a single cell type that falls within the scope of the claims. Absent a description of other cell types and methods for obtaining them, the specification fails to disclose how to obtain the full scope of cell compositions covered by the claims. Many of the cell types included within the claimed cell composition may not even exist in nature. If they do exist, the specification does not provide guidance for isolating them. Furthermore, given that the claimed populations would have widely variant phenotypes, the specification further fails to disclose how to use the scope of cell compositions covered by the claims.

In response to the enablement rejection, Applicants argue, at page 7, paragraph 1 of the response, that the specification provides support for a population of cells enriched for RS cells. However, given the lack of a definition for the term "RS cell" as discussed in detail above, the skilled artisan would not interpret the term to refer to any particular structural or functional properties of the claimed cells. Thus, the remainder of the claim must be relied upon to further limit the claimed cell composition to one comprising a defined cell type. However, as claimed, the only limitation placed on the "RS cell" is that the claimed composition must comprise 95% of them. The claim does not limit the RS cell to any particular structure. Where the claim recites "cells within said population express ..." the claim is not referring to RS cells, and thus in no way limits the cell type to anything specific.

At page 7, paragraph 1 of the response, Applicants assert that the skilled artisan would have been able to practice the invention commensurate with the scope of the claims without undue experimentation. However, no support is offered for this assertion.

At page 7, paragraph 2 of the response, Applicants assert that one skilled in the art would have been able to produce a population of cells enriched for RS cells using the series of unique RS surface epitopes to distinguish and isolate RS cells from a population of MSCs. However, as discussed in detail above, the claims do not require the **RS cells** to express **any** of the polypeptides recited in the claims. The presence of other non-RS cells expressing just one of the recited polypeptides would satisfy the claim limitation.

At page 7, paragraph 2 of the response, Applicants assert that the specification provides the unique RS polypeptides and surface markers useful for arriving at the cell population of the present invention. However, for the reasons discussed in detail above, the claims are not directed to compositions comprising the cell type described in the specification. As written, the claims do not require the presence of the cell type described in the specification, i.e. cells that have a defined protein expression profile, specific morphological features, the specific physical properties used in their isolation, specific multilineage potential, etc. The cell type described in the specification is described in terms of the manner in which it was obtained, its size, and its protein expression profile. However, these limitations do not appear in the claims and the specification does not **define** the term "RS cell" having any particular protein expression profile or as having any particular size. Where the claims recite "RS cells" there is nothing to impart the specific structural features described in the specification. Limitations discussed in the specification cannot be imported into the claims.

Given the limited guidance provided in the specification for obtaining and determining how to use the wide variety of cell compositions covered by the claims, the lack of applicable working examples directed to cell types other than the RS-1 and RS-2 cells mentioned in the specification (obtaining and

using), and the unpredictability for finding the various cell types covered by the claims in any tissue of the human body, undue experimentation would have been required for one skilled in the art to produce the full scope of the claimed cell compositions and determine how to use the widely variant compositions.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 stand rejected under 35 U.S.C. 102(b) as being anticipated by Bruder et al. (1997, J. Cell. Biochem. 64: 278-294), for reasons of record set forth in the Office Actions of 1/15/04 and 8/11/04.

At page 9, paragraphs 1 and 2 of the response, Applicants assert that the present invention relates to a population of cells enriched for human RS cells, that the claimed cell composition is **more homogenous** than the hMSCs disclosed by Bruder et al., and that Bruder must describe each and every element of the claims. No support is offered for the assertion that the claimed cell composition is more homogeneous than the hMSCs disclosed by Bruder. Contrary to this assertion, the **claimed** cell compositions are not directed to a composition that is more homogeneous than the hMSCs disclosed by Bruder et al. For the reasons discussed in detail above the limitation referring to "RS cells" does not impart any specific structural or functional property to the cells that make up the composition. Bruder et al. discloses purified human mesenchymal stem cells and further disclose that they obtain a near **homogeneous** population of spindle-shaped, rapidly dividing cells (page 290, column 2, paragraph 1). These cells retain the MSC phenotype. It is maintained that marker polypeptides are routinely used to identify a particular cell type, which itself demonstrates that the expression of particular markers are considered an inherent and identifying property of a particular cell type. Deans et al. (2000, not relied

upon for the rejection) discloses a number of properties that are inherent to human mesenchymal stem cells. For example, the reference discloses that human mesenchymal stem cells express transferrin receptor (CD71), as recited in Claim 1 and CD104, as recited in Claim 2 (see Table 1 at page 880). Thus, Bruder et al. discloses a cell population wherein "cells within said population express one or more" of the polypeptides recited in the claims. Furthermore, the cell population is disclosed as being near **homogeneous** which is sufficient to meet the limitation that "95% of the cells in said population are RS cells," given that the term "RS cell" is not defined and therefore does not refer to any particular set of cellular properties and further in view of the fact that the term "RS cell" is used in the specification to admittedly refer to a heterogeneous cell population and thus does not refer to a single cell type. Nothing more is required to meet the present claim limitations.

At page 9, paragraph 4 of the response, Applicants assert that the hMSCs described in Bruder et al. is actually a mixed population of cells which cannot contain 95% RS cells. Applicants further assert that Bruder does not teach a subpopulation of RS cells, "yet alone an enriched population of cells having about 95% RS cells." Contrary to this assertion, Bruder et al. need not use the term "RS cell" to teach a cell composition that meets all the limitations of the claim, because the term "RS cell" does not impart any structural or functional limitation to the claimed cell composition. For the reasons presented herein above and in the previous Office Actions, Bruder et al. disclose a cell composition that meets all the limitations of the claims. Nothing more is required.

Claims 1-3 stand rejected under 35 U.S.C. 102(b) as being anticipated by Pittenger et al. (1999, Science 284: 143-147), for reasons of record set forth in the Office Actions of 1/15/04 and 8/11/04.

Pittenger et al. (1999) disclose an isolated population of homogeneous human mesenchymal stem cells from bone marrow taken from the iliac crest (page 143, column 3). The legend to Figure 1 states that at 14 days, the cells were 95 to 99% homogeneous and were negative for reactivity to antigens CD14,

CD34, or CD45. The figure legend also states that homogeneity and reproducibility of the isolation procedure was demonstrated by flow cytometry (see Figure 1D). At page 144, column 1, the reference states that the "isolated cultured mesenchymal cells comprised a single phenotypic population (95 and 98% homogeneous at passages 1 and 2, respectively) by flow cytometric analysis of expressed surface antigens." The cells were uniformly positive for SH2, SH3, CD29, CD44, CD71, CD90, CD106, CD120a, CD124, and many other surface proteins (page 144, column 1). CD71 is another name for transferrin receptor. Thus, it is clear that the cells disclosed by Pittenger meet the limitation of Claim 1, which recites that the cells "express one or more polypeptides selected from the group consisting of VEGF receptor-2 (FLK-1), TRK (an NGF receptor), transferrin receptor, and annexin II (lipocortin 2)." The expression of the particular polypeptides, such as FLK-1, TRK, transferrin receptor, and annexin II is considered an inherent property of a known cell type. In the decision of *In re Spada*, 15 USPQ2d 1655 (CAFC 1990) the court points out that discovery of a new property or use of a previously known composition, even if unobvious from prior art, cannot impart patentability to claims to known compositions.

Thus, the claimed invention is disclosed in the prior art.

At page 10, paragraph 2 of the response, Applicants assert that Pittenger "does not teach a subset population of mesenchymal stem cells" Applicants further assert that the reference does not teach "an enriched population of RS cells." Contrary to Applicants' assertion, the claims are not directed to "a subset population of mesenchymal stem cells." Rather, Claim 1 recites "a population of cells enriched for human small and rapidly self-renewing stem cells (RS), wherein about 95% of the cells in said population are RS cells, further wherein the cells within said population express one or more polypeptides selected from the group consisting of VEGF receptor-2 (FLK-1), TRK (an NGF receptor), transferrin receptor, and annexin II (lipocortin 2)." As discussed above, Pittenger need not use the term "RS cell" to teach a cell composition that meets all the limitations of the claim, because the term "RS cell" does not impart any

structural or functional limitation to the claimed cell composition. Pittenger et al. explicitly discloses a cell composition comprising "a single phenotypic population (95 and 98% homogeneous at passages 1 and 2 respectively)" (page 144, column 1) and that the cells were "uniformly positive" for a number of markers including CD71 (transferrin receptor) (page 144, column 1). Deans et al. (2000, not relied upon for the rejection) discloses a number of properties that are inherent to human mesenchymal stem cells. For example, the reference discloses that human mesenchymal stem cells express CD104, as recited in Claim 2 (see Table 1 at page 880). Thus, for the reasons presented herein above and in the previous Office Actions, Pittenger et al. disclose a cell composition that meets all the limitations of the claims. Nothing more is required.

At page 10, paragraph 2 of the response, Applicants assert that Pittenger does not disclose a population of MSCs that are free of mMSCs. However, Applicants are arguing limitations that are not in the claims. The claims are not directed to a population that is free of mMSCs. Applicants further assert that Pittenger does not teach a subset population of cells within a population of MSCs. Applicants are again arguing limitations that are not in the claims. The claims do not refer to a subset population of cells within a population of MSCs. No such limitation appears in the claims.

The rejections of Claim 9 under 35 U.S.C. 102(b) are withdrawn in view of the amendment to the claim which includes the newly added limitation reciting that "about 95% of the cells in said population are RS cells" which, when taken in combination with the limitation "and said RS cells are about seven microns in diameter" implies that 95% of the cells in the claimed population are 7 microns in diameter. The cited references do not disclose a cell population where 95% of the cells are 7 microns in diameter. Claim 9 is, however, subject to other rejections.

Conclusion

No claims are allowable.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER